

## Comparative Study on the Efficiency of Various Binder Combinations for Metformin Tablets.

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## Research Article

## ABSTRACT

Metformin hydrochloride is widely used as an oral anti hypoglycemic agent. But it is difficult to formulate by direct compression method because of its poor compaction properties and its crystalline nature. The present study target for a better combination of binders that produces metformin tablets with unique results. The granulation is done using binder combination of gelatin, PVP K 30, HPMC, Cross Povidone, starch and Kyron-T 314. The wet granulation method is selected for the formulation of metformin tablets and the formulated tablets were evaluated for their hardness, friability, disintegration, content uniformity and dissolution profiles with USP type II apparatus at 100 rpm in pH 6.8 phosphate buffer solution. The Formulation F2 (containing gelatin and HPMC as binders) demonstrated unique results than the other formulations. The formulation F5 (containing gelatin and Kyron-T 314 as binders) shows faster disintegration than the other formulations but shows least hardness.

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## INTRODUCTION

Solid-dosage forms encompass the largest category of dosage forms that are clinically used. There are several types of tablet solid dosage forms that are designed to optimise the absorption rate of the drug, increase the ease of administration by the patient, control the rate and site of drug absorption and mask the taste of a therapeutic agent. The formulation of tablets involves the use of several components, each of which is present to facilitate the manufacture or to control the biological performance of the dosage form [1,2,3].

Metformin hydrochloride is 1, 1-dimethyl biguanide hydrochloride which comes under BCS class III and it is also used for the management of type 2 diabetes mellitus [4,5]. Due to its crystalline nature, metformin has poor compression property there by sticking occurs, to overcome the problem associated with, it is designed to know the efficiency of the various binders like PVP K 30, starch, HPMC, Cross Povidon, Kyron-T 314 the present research was carried out.

Since, the drug Metformin is crystalline in nature its compressability is poor so this drug requires to granulate which improves the flow property and content uniformity as well. Wet granulation technique is preferred since dry granulation is not possible because of its poor compressibility. wet granulation is one which is more widely used for granulation [6]. Which involves the addition of binder in a paste form which makes the drug and other ingredient a coherent mass which on further sieving gives granules which are loaded into a hot air oven to remove the moisture content. Thus obtained granules are passed through sieve number 12/20. The obtained granules and the fines are taken in appropriate ratio to reduce the porosity. Hence, the wet granulation is preferred. Metformin 500 mg tablets have been formulated by using wet granulation technique and evaluated [5].

The granulation is done using different binder combinations. The binders used are PVP K 30, HPMC, Cross Povidone, Starch and Kyron-T 314 [7]. Gelatin is used as a common binder in all the formulations (F1, F2, F3, F4, F5), where the second binder is altered.

MATERIALS AND METHODS

Materials

Metformin hydrochloride is received from Arabindo Pharma Ltd, India. Gelatin, starch is obtained from Remidex Pharma, India, PVP K 30 , methyl paraben , propyl paraben , magnesium stearate is supplied by Caplein Point Laboratories, Puducherry. Aerosol, Talc, Kyron-T 314 is gifted by Coral Pharma chem, Allahabad. All the other reagents were of analytical grade.

Methods

Preparation of Metformin Hydrochloride Tablets

The metformin hydrochloride tablets were prepared by wet granulation technique. The composition is as given in the (Table 1). Prescribed quantity of the metformin drug is weighed and passed through sieve number 20. The binder paste is prepared using combination of 2 binders as shown in the (Table 1) with purified water. Thus prepared binder paste is mixed with the metformin, methyl paraben and propyl paraben until a coherent mass is formed. The above mass is passed through sieve number 20 . The granules obtained are dried using hot air oven. Thus dried granules sieved using 12/20 sieve. To this granules obtained Magnesium stearate, talc and aerosil are added followed by compression<sup>[4]</sup>.

Table 1: Various Formulations of Metformin Hydrochloride tablets

| Formulation      | F 1     | F2      | F3      | F4      | F5      |
|------------------|---------|---------|---------|---------|---------|
| Metformin        | 500 mg  | 500 mg  | 500 mg  | 500 mg  | 500 mg  |
| PVP K 30         | 3.5 %   | -       | -       | -       | -       |
| HPMC             | -       | 3.5%    | -       | -       | -       |
| Cross povidone   | -       | -       | 3.5%    | -       | -       |
| Starch           | -       | -       | -       | 3.5 %   | -       |
| Kyron - T        | -       | -       | -       | -       | 3.5 %   |
| Gelatin          | 2.5 %   | 2.5 %   | 2.5 %   | 2.5 %   | 2.5 %   |
| Methyl Paraben   | 0.015 % | 0.015 % | 0.015 % | 0.015 % | 0.015 % |
| Propyl Paraben   | 0.015 % | 0.015 % | 0.015 % | 0.015 % | 0.015 % |
| MagnesiumSterate | 1 %     | 1 %     | 1 %     | 1 %     | 1 %     |
| Aerosil          | 3 %     | 3 %     | 3 %     | 3 %     | 3 %     |
| Talc             | 1 %     | 1 %     | 1 %     | 1 %     | 1 %     |

Evaluation Pre Compression Studies

Bulk and Tapped Densities

Exactly 50 gm of metformin hydrochloride granules was weighed and transferred into a 100 mL measuring cylinder. The cylinder was dropped on a wooden platform from a height of 2.5 cm three times at 2 seconds interval. The volume filled by the metformin hydrochloride granules was considered as the bulk volume. The cylinder was then tapped on the wooden platform until the volume occupied by the metformin hydrochloride granules remained constant. This was repeated three times more with the same drug. The data generated was used in calculating the Carr’s compressibility index (CI) and Hausner’s ratio (HR) for the metformin<sup>[8]</sup>.

$$\text{Carr's Index} = 100(\text{TD}-\text{BD}) / \text{TD}$$

$$\text{Hausner's Ratio} = \text{TD}/\text{BD}$$

Where,

TD is Tapped Density , BD is Bulk Density

Angle of Repose

50 gm of the metformin granules was placed in a funnel whose orifice is closed using a cotton plug, which had a distance of 10 cm from the flat surface. The content was then allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) and the radius of the heap (r) were noted <sup>[8]</sup>.

$$\text{The angle of repose } (\theta) \text{ was calculated as } \theta = \tan^{-1} h/r$$

#### Moisture Content

1 gm of the granules was placed in a crucible and dried to constant weight in a hot air oven. The moisture content (MC) was estimated from the difference between the initial ( $W_i$ ) and final weight ( $W_f$ ) of the granules. This is expressed in percentage and calculated as:

$$\text{Moisture Content} = 100 (W_i - W_f) / W_i$$

Where,

$W_i$  is initial weight of the granules  $W_f$  is final weight of the granules

#### Post Compression Studies

##### Thickness

10 tablets were randomly selected and the thickness of these tablets is measured using vernier calipers (Mitutogo vernier calipers, Japan) and the mean of these readings was taken.

##### Weight Variation

20 tablets were weighed individually and also collectively. The average weight was calculated and the individual tablet weight was also determined. Each individual value was checked whether it lies in the limit of  $\pm 5\%$  deviation from the average value.

##### Hardness

The hardness test was carried out for 10 tablets by using Monsanto Hardness Tester (Model: Mht - 20, USA). The average of 3 determinations for each batch was noted.

##### Friability

The Friability of 10 tablets was determined using Friabilator, (Electro lab-EF<sub>2</sub> USP/USA). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed tablets were placed in the friabilator and were operated for 100 revolutions. Tablets were dedusted using a soft cloth and weighed again. The friability (F) is given by the formula,

$$\text{Friability} = (1 - W_i / W_f) \times 100$$

Where,

$W_i$  is initial weight of the tablet,  $W_f$  is final weight of tablet

##### Disintegration Test

The disintegration time of tablets was determined according to the method described in the British Pharmacopoeia 1998. Six tablets were placed in each compartment of the disintegration apparatus, with water thermo stated at  $37 \pm 1$  °C as the medium. The tablets were considered to have passed the test after the 6 tablets passed through the mesh of the apparatus in 15 minutes.

##### Assay

20 tablets were weighed and powdered. Quantity equivalent to 0.1 g of Metformin was weighed and transferred to 100 mL beaker containing 70 mL water, stirred for 15 min and made the volume to 100 mL. 10 mL from the above solution is diluted to 100 mL with water and measured the absorbance at 233 nm using UV spectrophotometer (UV 1600)<sup>[9,10]</sup>.

##### Dissolution Test

The dissolution test was performed using TDT-08L USP type II (Electro lab, Mumbai, India) apparatus using 900 mL of 6.8 pH buffers as medium at a temperature of  $37 \pm 0.5$ °C with 100 rpm for 120 minutes. The samples are collected at regular intervals (10, 20, 30,40,50,60, respectively) and thus collected samples were diluted with the above media and the absorbance is determined at 233 nm using UV spectrophotometer (UV1800, Shimadzu, Malaysia) <sup>[9]</sup>.

RESULTS AND DISCUSSION

From the results depicted in the Table 2 all the five formulations show good flow properties and passes the preformulation tests. The formulation F2 is prepared using a binder combination of gelatin and HPMC; it shows hardness of about  $6.7 \pm 0.75 \text{ kg/cm}^2$  which is good enough to resist the mechanical shocks. The friability is found to be  $0.46 \pm 0.05\%$ , which is in the limits and this is due to the hardness of the tablet obtained by using a combination of gelatin and HPMC as binding agents. An assay value of 99.2% is observed which is good enough to make the drug with stand in the therapeutic range. The dissolution profile shown in the Table 3 a release of 99% is obtained because of the HPMC present in the formulation which contains cellulose ethers which are hygroscopic and it absorbs moisture from surroundings and release the drug bound to it. This efficiency of it make use of it as binder of choice.

Table 2: Pre-compression Parameters for Metformin hydrochloride Granules.

| S.NO | TEST                  | F 1     | F 2     | F 3     | F 4     | F 5     |
|------|-----------------------|---------|---------|---------|---------|---------|
| 1    | Bulk density(g/ml)    | 0.5405  | 0.5137  | 0.5213  | 0.4941  | 0.5148  |
| 2.   | Tapped density (g/ml) | 0.6717  | 0.6456  | 0.6417  | 0.6107  | 0.6013  |
| 3.   | Hausner's ratio       | 1.2427  | 1.2567  | 1.2309  | 1.2359  | 1.1680  |
| 4.   | Carr's index          | 19.5325 | 20.4306 | 18.7626 | 19.0928 | 14.3854 |
| 5.   | Moisture content (%)  | 4       | 4       | 4       | 5       | 5       |
| 6    | Angle of repose (°)   | 26.51   | 25.35   | 24.63   | 24.14   | 23.50   |
| 7.   | Relative density      | 0.804   | 0.795   | 0.812   | 0.809   | 0.856   |
| 8.   | Porosity              | 0.196   | 0.205   | 0.188   | 0.191   | 0.144   |

Table 3: Post Compression Studies of Metformin Hydrochloride Tablets

| TEST                           | F 1       | F 2       | F 3       | F 4       | F 5       |
|--------------------------------|-----------|-----------|-----------|-----------|-----------|
| Hardness (kg/cm <sup>2</sup> ) | 5.9±0.23  | 6.7±0.75  | 6.4±0.17  | 6.0±0.35  | 3.8±0.31  |
| Friability (%)                 | 0.57±0.04 | 0.46±0.05 | 0.61±0.02 | 0.66±0.04 | 0.87±0.04 |
| Weight variation (mg)          | 551±3.52  | 549±3.1   | 544±4.1   | 550±2.1   | 546±1.7   |
| Disintegration time(min)       | 10.5±0.45 | 12.4±0.75 | 13.1±0.65 | 13.6±0.35 | 5.5±0.9   |
| Assay (%)                      | 98.6      | 99.2      | 97.8      | 98.2      | 97.7      |
| % drug release after 120 min   | 96.9%     | 99.%      | 95.7%     | 96.2%     | 97.2%     |

The formulations F1, F3, F4 were prepared using the binder gelatin in combination with PVP K 30, Cross Povidon, Starch respectively. This formulations had given a hardness in the range of 5.9–6.4 kg/cm<sup>2</sup>, which provide a good physical resistance for the Metformin tablets from physical shocks. The friability is ranging between 0.57–0.66 % which is below 1 showing that this formulations passes the friability test. The assay values are ranging between 97.8% and 98.6%. The disintegration time is below 15 min that is in the acceptable range. The drug release profile as shown in the Table.3 and Figure 1 is in between 95.7–96.9%.

The Formulation F5 contains Kyron-T 314 and gelatin binder combination which give a very poor hardness of about 3.8±0.31 kg/cm<sup>2</sup> as shown in the Figure 2, which is not in the acceptable range and capping problem is observed which is due to the in efficiency of Kyron-T 314 as a binder. But a fast disintegration is observed which is below 5 min 25 sec, this may be useful when an immediate release of drug is required. So a combination of another binder with the Kyron-T 314 can produce a fast dissolving Metformin Tablets.

CONCLUSION

In conclusion the Metformin Hydrochloride tablets were successfully prepared by wet granulation technique. The formulation F2 was found to give unique results; this was due to the presence of gelatin and HPMC binders combination. The formulation F5 had shown less hardness due to the presence of Kyron-T 314 as binder. A combination of gelatin and HPMC was found to be an effective binder in preparation of Metformin Hydrochloride tablets by wet granulation technique.

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Figure 1: Dissolution profiles of the Formulations ( F1-F5)

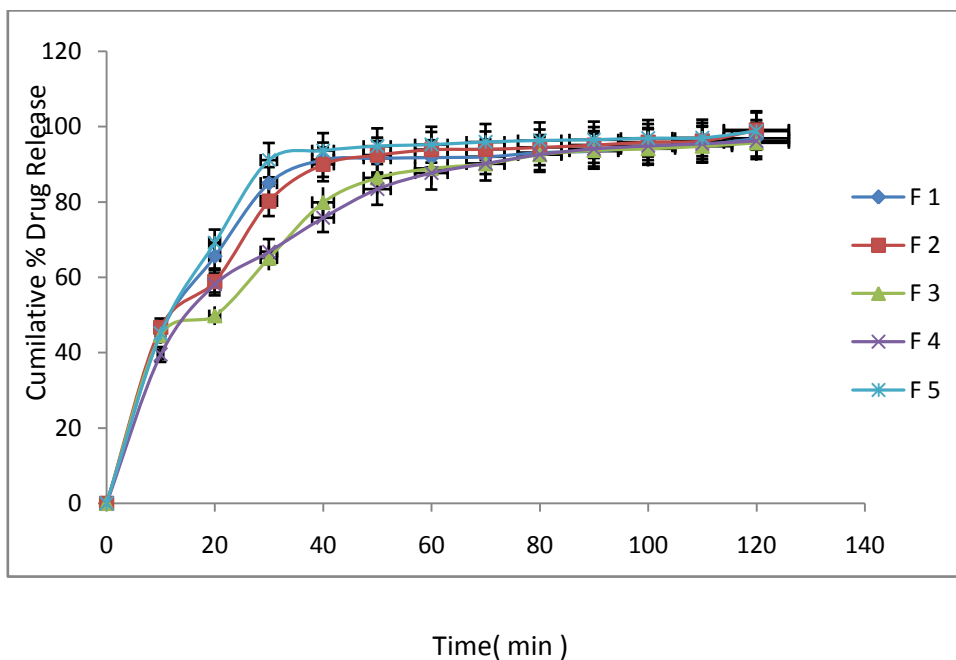
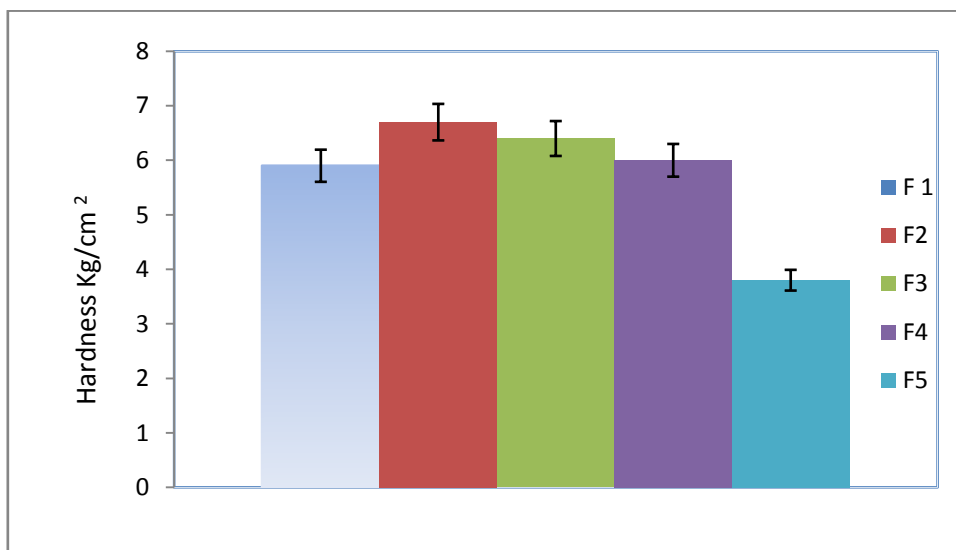


Figure 2: Represents Hardness of the developed Formulations



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